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Effects of Dehydration on Cardiovascular Reponses and Electrolytes Following Hypertonic Saline Dextran Treatment for Moderate Hemorrhage

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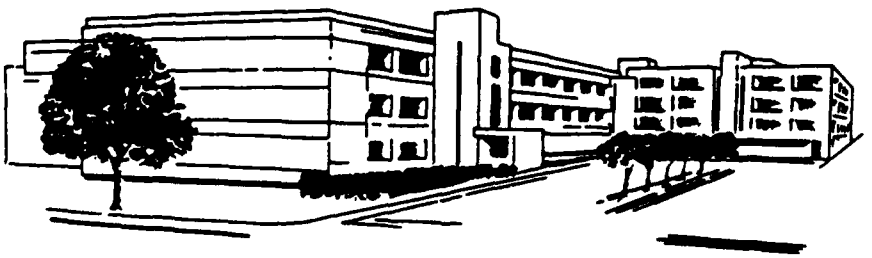

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Effects of Dehydration on Cardiovascular Responses and Electrolytes Following Hypertonic Saline Dextran Treatment for Moderate Hemorrhage. (Institute Report 426)--C.Wade, et al

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The efficacy of hypertonic saline/dextran (HSD) for treating hemorrhage in the presence of dehydration was evaluated in conscious swine. Following surgical preparation, animals were euhydrated or dehydrated for 24 hr or 48 hr. Dehydration resulted in a reduction in body weight and increased plasma osmolality and sodium levels, but did not alter plasma volume. Animals were bled 25 ml/kg/60 min and treated with HSD (4 ml/kg/1 min, 7.5% NaCl and 6% Dextran 70). HSD immediately rectified the decreases in mean arterial pressure and cardiac output incurred during hemorrhage. There were parallel increases in plasma osmolality and sodium concentrations which were offset by the initial differences due to dehydration. All groups showed equivalent decreases in hematocrit, hemoglobin and protein. Given these results, we concluded that dehydration does not compromise the efficacy of HSD as a resuscitation treatment for hemorrhagic shock.

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ABSTRACT

The efficacy of hypertonic saline/dextran (HSD) for treating hemorrhage in the presence of dehydration was evaluated in conscious swine. Following surgical preparation, animals were euhydrated or dehydrated for 24 hr or 48 hr. Dehydration resulted in a reduction in body weight and increased plasma osmolality and sodium levels, but did not alter plasma volume. Animals were bled 25 ml/kg/60 min and treated with HSD (4 ml/kg/1 min, 7.5% NaCl and 6% Dextran 70). HSD immediately rectified the decreases in mean arterial pressure and cardiac output incurred during hemorrhage. There were parallel increases in plasma osmolality and sodium concentrations which were offset by the initial differences due to dehydration. All groups showed equivalent decreases in hematocrit, hemoglobin and protein. Given these results, we concluded that dehydration does not compromise the efficacy of HSD as a resuscitation treatment for hemorrhagic shock.

Effect of Dehydration on Cardiovascular Responses and Electrolytes Following Hypertonic Saline Dextran Treatment for Moderate Hemorrhage. -- Wade et al.

INTRODUCTION

Hypertonic/oncotic solutions (HSD) have recently been demonstrated to be efficacious in the treatment of hemorrhagic hypotension (1-5). These solutions increase vascular volume by mobilizing fluid from the extravascular space, primarily the cellular compartment (3,5). Because the expansion in blood volume is accompanied by an increase in plasma sodium concentration and osmolality (1-5), the advisability of administering these solutions to dehydrated patients could be questioned.

People are often dehydrated, either from inadequate fluid ingestion or from fluid loss due to sweating (6-9). Furthermore, people often voluntarily dehydrate, decreasing their total body water by over 2.5% (6-9). Since dehydration causes a decrease in extracellular (ECF) and intracellular (ICF) fluid volumes, compensation to hemorrhage may be severely limited in the presence of dehydration (10,11). Treatment with HSD could be ineffective, because HSD induces plasma volume expansion by drawing fluid from the ECF and ICF compartments. In addition, since dehydration causes an elevated plasma osmolality (Posm) and sodium concentration (PNa), further increases in Posm and PNa from HSD treatment could actually be detrimental to dehydrated, hemorrhagic trauma victims. We performed the present studies in conscious immature swine to assess whether dehydration altered the cardiovascular and plasma electrolyte responses to resuscitation of a moderate hemorrhage with HSD.

METHODS

Seventeen immature Yorkshire pigs were obtained from a commercial breeder and housed in a common laboratory facility for one to three weeks prior to experimentation. During this period, and subsequently, animals were fed a commercial chow and provided water ad libitum. For three to five days prior to surgery, the animals were transported daily to the laboratory and familiarized with the surroundings, personnel and handling procedures. The animals were trained to rest

quietly in a modified Pavlov sling for 60 minutes. Training continued one day post-operatively until the beginning of the experiment.

Surgical Procedures

Seven days prior to the experiments, animals were prepared surgically using aseptic procedures. Details of these procedures are presented elsewhere (3,12,13). Briefly, the animals were administered a preanesthetic injection of 0.8 mg/kg atropine sulfate, 2.2 mg/kg ketamine HCl and 2.2 mg/kg xylazine. Halothane anesthesia was induced by a snout mask and maintained with an endotracheal tube. The animals were splenectomized, and a carotid arterial catheter implanted. A Swan Ganz catheter was positioned in the pulmonary artery with placement confirmed by observing the desired pressure wave form. All catheters were exteriorized, secured to the skin, and covered with a velcro patch. Each animal was given an intramuscular injection of 40 mg gentamicin. Animals were observed throughout the post-operative recovery period, then returned to their holding cages and provided food and water.

Experimental protocol

Following an overnight fast with free access to water, the animal was weighed, transported to the laboratory and placed in the sling. Catheters were cleared of stagnant blood and saline, flushed and connected to appropriate transducers to measure arterial pressures and cardiac output. Following a 60 min period of quiet rest, hemodynamic measurements and a blood sample were obtained. These procedures were repeated after 10 min and the mean of these two values represented the pre-dehydration values. Upon completion of these control measurements, the catheters were flushed with normal saline and again secured to the skin. The animal was then placed in a metabolic cage for the next 48 hours. Animals were randomly assigned to one of three groups: **Euhydrated** (E): provided free access to water over the 48 hr period (n=5). **Dehydrated 24 hours** (D24): water provided the first 24 hours and removed the next 24 hours (n=6). **Dehydrated 48 hours** (D48); water removed for the full 48 hour period (n=6). Food was provided ad libitum until the final 12 hours.

Following the 12 hour fast, the animal was again placed in the sling and the catheters cleared, flushed, and connected for hemodynamic measurements and withdrawal of blood samples. After a 30 min control period, measurements were taken for the post dehydration sample. The animals were hemorrhaged 25 ml/kg over 60 min via the arterial catheter. Immediately upon completion of the hemorrhage, another blood sample was taken and the animal rapidly (over 1 min) treated with 4 ml/kg of hypertonic saline/dextran (HSD) (7.5% NaCl and 6% Dextran® 70, Pharmacia, Uppsala, Sweden, LOT #54845). Hemodynamic measurements and blood samples were taken at 5, 15, 30, 60, 120 and 180 min post administration of the HSD. Data are only presented through the first 60 min after resuscitation (see statistical analysis).

Blood Analysis

Hemoglobin concentration was measured with an Instrumentation Laboratory cooximeter, Model 282. Following centrifugation plasma sodium and potassium concentrations (Cobas autoanalyzer), osmolality (Advanced Instruments, Model 3D II) and total protein content (American optical refractometer) were measured. Hematocrit was determined in duplicate by the microcapillary method. Blood lactate and glucose levels were measured using a Cobas autoanalyzer and Sigma system test kits.

Hemodynamic Measurements

Mean arterial pressure was calculated from measurements of systolic and diastolic pressures. Heart rate was measured from the blood pressure tracings. Cardiac output was measured by the thermodilution technique. The injection was 5 ml of normal saline at room temperature. Successive measurements of cardiac output were made until two consecutive recordings differed by no more than 0.2 L/min.

Statistical Analysis

Covariant analysis of variance with adjustments for repeated measures was used to determine differences due to hydration status and over time (in response to both hemorrhage and HSD treatment). The value at the end of hemorrhage served as the covariant to compare the effects of resuscitation with HSD. Differences

between individual means were tested by the Newman-Keuls procedure when appropriate. Changes were considered significant when $p<0.05$. As animals were lost to follow-up due to deaths, the statistical analyses were confined to the first 60 min following treatment. Values in the text are means + SEM.

RESULTS

Survival

Of the euhydrated animals, 100% survived until completion of the experiment (180 min post treatment). Within three hours of treatment, two (33%) of the animals dehydrated for 24 hours had died as had three (50%) of those dehydrated for 48 hours. In preliminary experiments without treatment, dehydrated animals (n=4) died following hemorrhage while all euhydrated animals (n=3) survived.

Dehydration Effects

Dehydration resulted in a statistically significant decrease in body weight which was greater in animals dehydrated for 48 hours than in animals dehydrated for 24 hours (Table I). Changes in body weights over the pre-experimental period were $+0.9\pm0.5$ (+5%), -1.0 ± 0.3 (-4%) and -1.7 ± 0.1 kg (-8%) for animals euhydrated (E), dehydrated 24 hr (D24), and dehydrated 48 hr (D48), respectively. Heart rate, mean arterial pressure, cardiac output and pulmonary artery pressure were not significantly altered by dehydration (Table I). Dehydration increased plasma sodium concentration, osmolality and total protein levels with greater changes with D48 than D24 (Table I). Plasma potassium levels of all three groups increased over time, but no effect of dehydration was noted. Hematocrit decreased over the observation period irrespective of fluid status with no difference between groups, while hemoglobin concentrations were unchanged. Blood glucose and lactate concentrations were not changed due to dehydration.

Hemorrhage Effects

Hemorrhage decreased mean arterial and cardiac output, while heart rate was not altered (Fig. 1). There was no effect of prior dehydration on the cardiovascular responses to hemorrhage. Hemorrhage significantly reduced hematocrit, hemoglobin and plasma

total protein levels, to the same extent in all three groups (Fig. 2). Plasma sodium and potassium concentrations were not changed during hemorrhage nor was plasma osmolality (Fig. 3). Blood glucose was increased during hemorrhage, with a greater increase in dehydrated animal (Fig. 4). Lactate concentrations were increased following hemorrhage, with a trend for greater increases in dehydrated animals (Fig. 4).

Resuscitation Effects

Administration of HSD produced a rapid rise in mean arterial pressure in all groups within the first 5 min (Fig. 1). This improvement, however, was sustained only in euhydrated animals (Fig. 1). In dehydrated animals, mean arterial pressure increased transiently after the injection of HSD, but then fell to values which were not different from values at the end of hemorrhage. Cardiac output was increased in all groups following the administration of HSD with no differences noted between groups (Fig. 1). Over time, cardiac output values regressed, but were still greater than the values at the end of hemorrhage. Injection of HSD reduced hematocrit, hemoglobin and plasma total protein levels to a similar degree in all groups (Fig. 2). After the initial decrease occurring immediately after treatment, there were no further changes.

Treatment with HSD increased plasma sodium by 9.1 ± 2.7, 10.2 ± 1.9 and 8.8 ± 2.5 mEq/l and osmolality by 22 ± 5, 17 ± 5 and 26 ± 3 mOsm/kg in E, D24 and D48 respectively (Fig. 3). Differences between the groups reflected initial differences due to dehydration. Over 60 min post treatment, plasma sodium concentration and osmolality decreased, but remained higher than levels at the end of hemorrhage. Plasma potassium concentration was reduced immediately after treatment with HSD in all groups, but subsequently increased (Fig. 3). After 60 min, however, the plasma potassium levels were still low compared to those measured at the end of hemorrhage.

Immediately following treatment, blood glucose concentrations were not altered, but 60 min after treatment they decreased to values that still exceeded those recorded during the pre-hemorrhage control period (Fig. 4). Increases in blood glucose incurred during hemorrhage were sustained through the post-treatment period with between-group differences persisting. Blood lactate concentrations increased in all groups

upon administration of HSD, and decreased over the subsequent 60 min.

DISCUSSION

Dehydration is characterized by a decrease in total body water and blood volume, accompanied by an increase in plasma electrolyte concentrations (6-9). These changes could compromise compensations to hemorrhage (10,11) and the benefits of subsequent treatment and resuscitation. In the present study, decreases in body weight of 4 and 8% after 24 and 48 hours of fluid deprivation indicate significant reductions in total body water. In humans decreases in total body water of this magnitude result in a reduced blood volume (6,9). However, indices of a blood volume change do not support a similar effect on vascular fluid volume in pigs. In contrast to the effects of dehydration observed in human plasma total protein concentration, hemoglobin levels and hematocrit were not changed significantly following dehydration, thus indicating a maintenance of the vascular volume in the pig. A similar maintenance of plasma volume during dehydration has been noted in baboons (14). Increases in the concentration of plasma sodium and osmolality were observed in dehydrated pigs. The increase in plasma osmolality in the absence of a decrease in blood volume suggests the water losses over the course of the dehydration came from fluid compartments other than the vascular space.

The decrease in extravascular water during dehydration could affect the compensatory transcapillary flux during hemorrhage and the mobilization of fluid into the vascular space after administration of HSD (3-5,11,15-17). Barrientos et al. (11) reported that the transcapillary reflux following hemorrhage was severely impaired in pigs by prior dehydration and resulted in an increase in mortality. At the end of hemorrhage in the present study, there was no difference between hydration groups in hemoglobin concentrations, plasma total protein levels or hematocrit, thereby indicating a similar degree of transcapillary fluid flux. The lack of difference in blood volume at the end of hemorrhage may be due in part to the greater increase in glucose levels in dehydrated animals. An increase in glucose concentration during hemorrhage is postulated to facilitate the movement of water from cells into the

extracellular space (18,19). Therefore, the movement of fluid into the vascular space during hemorrhage appears to be independent of hydration status.

Administering HSD produces a rapid expansion of blood volume by drawing fluid from the extravascular space up an osmotic-oncotic concentration gradient (3-5,16,17). Dehydration could reduce the availability of fluid for mobilization from extravascular compartments. Following HSD injection, the expansion of blood volume, as indicated by changes in hematocrit, hemoglobin and total plasma protein levels, was independent of hydration status and sustained over the one hour following treatment. Thus, the decrease in extravascular fluid due to dehydration did not affect the expansion of blood volume induced by HSD treatment.

Following dehydration, there was a significant difference in plasma sodium concentration and osmolality among groups. These differences among groups persisted throughout the experiment. Administration of HSD produced further increases in plasma sodium levels and osmolality. These increases facilitate the movement of fluid into the vascular space (16). In dehydrated animals, the extracellular space, specifically the interstitial compartment, was reduced as indicated by the increase in plasma sodium and osmolality. The injection of HSD into a smaller volume of distribution should have resulted in a greater increases in osmolality and sodium in dehydrated animals, however the increases were similar in all groups. This finding suggests that movement of water from the cellular compartment in response to HSD administration was similar and independent of hydration status. Thus the degree of cellular dehydration following HSD is greater in the animals deprived of fluid.

Hemodynamic function was not altered by fluid deprivation, and the response to hemorrhage was similar in all groups. The administration of HSD improved hemodynamic function as has been reported by us and others in a variety of species (3-5). Furthermore, in the present study, immediate improvements in hemodynamic functions were independent of hydration status. In dehydrated animals, the improvement in mean arterial pressure was not sustained beyond 30 min. The failure to sustain the HSD-induced increase in mean arterial pressure in dehydrated pigs was similar to that previously reported for pigs treated following

severe hemorrhage (3). In contrast, the improvement in blood pressure did persist in euhydrated animals, similar to the response noted in other species following treatment with HSD (4,5,16). The maintenance of blood pressure following HSD administration thus appears to be affected by hydration status reflecting that a given volume of hemorrhage is a relatively more severe event in dehydrated as compared to euhydrated animals.

Pulmonary artery pressure (PAP) decreased during hemorrhage, an effect reversed by HSD. Similar responses have been reported by Kramer et al. (5). The increase in pulmonary artery pressure may reflect HSD induced changes in blood volume (5) as well as a direct effect on myocardial function (20). Of particular importance, the present study showed that hydration state had no effect on the improvement in PAP following HSD administration.

Cardiac output increased immediately after the administration of HSD but fell over time. The initial increase in cardiac output is suggested to be a function of the expansion of blood volume induced by administering HSD (5,16,17). However, the decrease in cardiac output following treatment was independent of blood volume, which remained constant. It has been suggested that other factors are contributing to the immediate increase in cardiac output and are not sustained over time (3,20). Kien and coworkers (20) demonstrated a direct effect of hyperosmotic saline in improving cardiac contractility which may play an important role in restoring cardiovascular function. The present study suggests that the response of cardiac output to HSD administration is associated with an expansion of blood volume, as well as an increase in plasma osmolality, irrespective of hydration status. Collectively, these changes enhance survival (3-5).

In summary, the present study shows that the administration of HSD to dehydrated pigs to treat hemorrhage is initially as effective as it is in euhydrated pigs. Hemodynamic function was improved following treatment with HSD irrespective of hydration status. However, the increases were not sustained in dehydrated animals. The increase in plasma osmolality and sodium concentration resulting from treatment with HSD were also similar in all groups, thus the final levels reflected the initial state of hydration. Improvements in cardiovascular function and blood

volume do not, however, assure survival. We observed a decrease in survival of dehydrated animals even though improvements in plasma volume and hemodynamic function occurred with HSD. This observation confirms earlier work (10,11) that hydration state at the time of hemorrhage is critical to subsequent survival even with adequate resuscitation of cardiovascular function. We concluded that dehydration does not compromise the efficacy of HSD as a resuscitation treatment for hemorrhagic hypotension.

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Table I

Changes in response to alteration of hydration status.

		Predehydration	Dehydration
Body Weight (kg)	E	19.1±0.93	20.0±1.43
	D24	23.0±0.79	22.0±0.74*
	D48	20.4±2.16	18.7±2.12*
Heart Rate (b/min)	E	133±4.5	123±2.9
	D24	158±11.0	155±8.3
	D48	136±9.0	138±6.6
Mean Arterial Pressure (mmHg)	E	115±5.8	114±4.3
	D24	114±5.5	108±6.3
	D48	112±6.36	104±4.9
Cardiac Output (l/min)	E	4.4±0.51	4.7±0.50
	D24	4.5±0.32	4.5±0.42
	D48	4.5±0.36	5.1±0.47
Pulmonary Artery Pressure (mmHg)	E	---	-4±6.4
	D24	---	-1±7.0
	D48	---	-8±11.0
Plasma Osmolality (mOsm/kg)	E	287±4.0	284±1.6
	D24	293±3.5	304±5.8*
	D48	287±1.7	320±6.6*
Plasma Sodium (mEq/l)	E	145.3±1.60	143.8±1.27
	D24	143.3±1.95	150.8±3.23*
	D48	143.0±0.77	155.5±5.96*
Plasma Potassium (mEq/l)	E	4.1±0.21	4.7±0.17
	D24	4.3±0.16	4.9±0.10
	D48	4.4±0.30	4.5±0.18
Blood Glucose	E	96±3.9	97±2.8
	D24	104±8.9	106±22.5
	D48	116±4.9	99±4.9
Blood Lactate (kg)	E	18.3±9.57	10.5±2.77
	D24	10.8±2.86	18.7±7.43
	D48	16.3±4.86	17.9±6.04
Hematocrit (%)	E	30.8±1.53	28.8±2.40
	D24	28.8±0.88	26.0±1.51
	D48	31.4±0.74	30.0±1.38

Table I (con't)

Changes in response to alteration of hydration status.

		Predehydration	Dehydration
Hemoglobin	E	9.1±0.58	7.6±0.48
	D24	9.5±0.06	8.3±0.42
	D48	9.1±0.41	10.5±0.24
Total Protein (mg/dl)	E	5.8±0.27	5.7±0.28
	D24	6.1±0.28	6.3±0.41
	D48	5.6±0.11	6.0±0.16

* Significantly different from pre hydration values, $P<0.05$.

Figure Legends

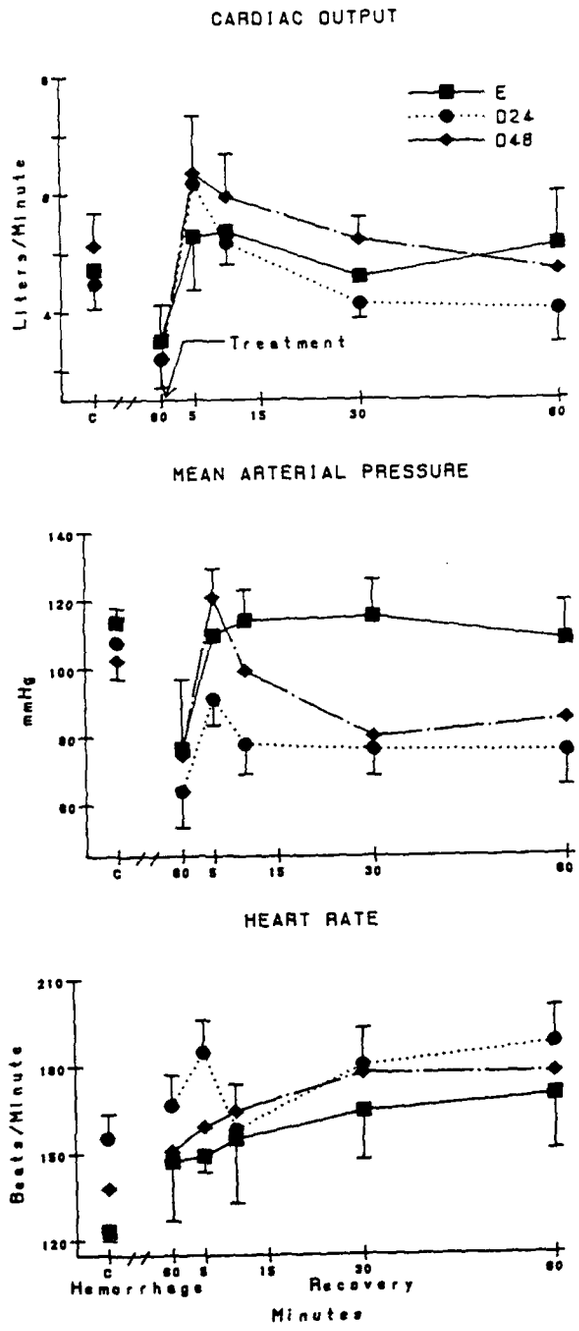

Figure 1: Hemodynamic responses to hemorrhage and subsequent resuscitation with HSD in pigs in varying states of hydration. E - euhydrated; D24 - dehydrated for 24 hrs; D48 - dehydration for 48 hrs.

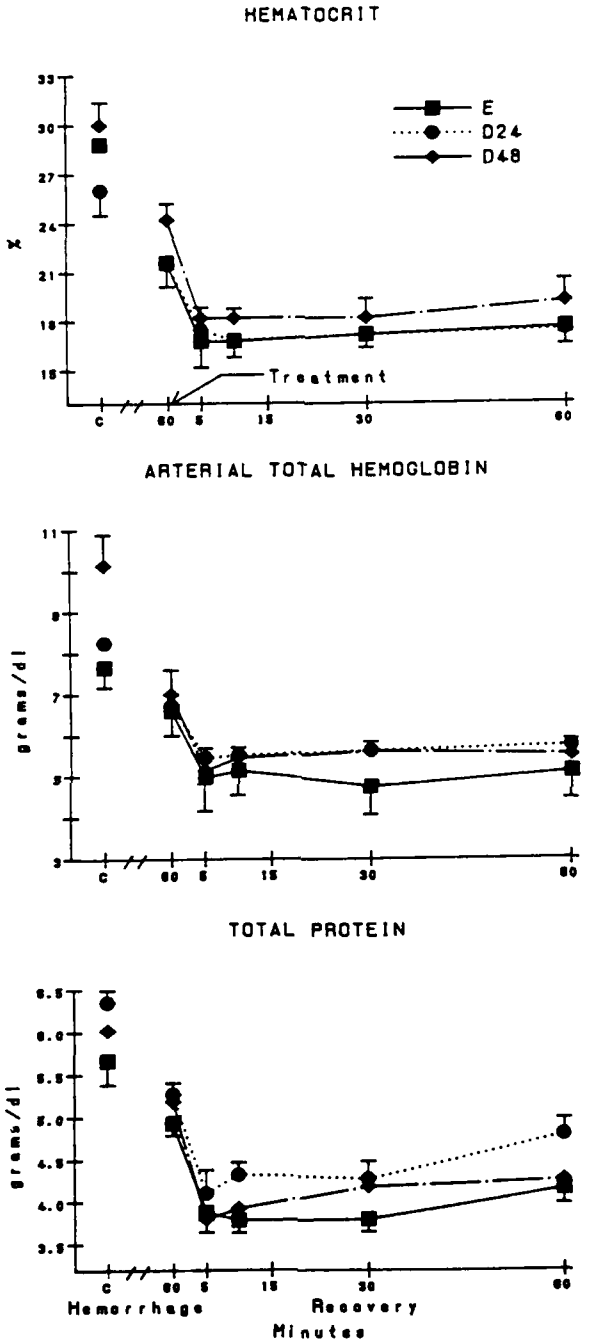

Figure 2: Responses of hematocrit, hemoglobin, and total protein to hemorrhage and subsequent resuscitation with HSD in pigs in various states of hydration. (See Figure 1 legend)

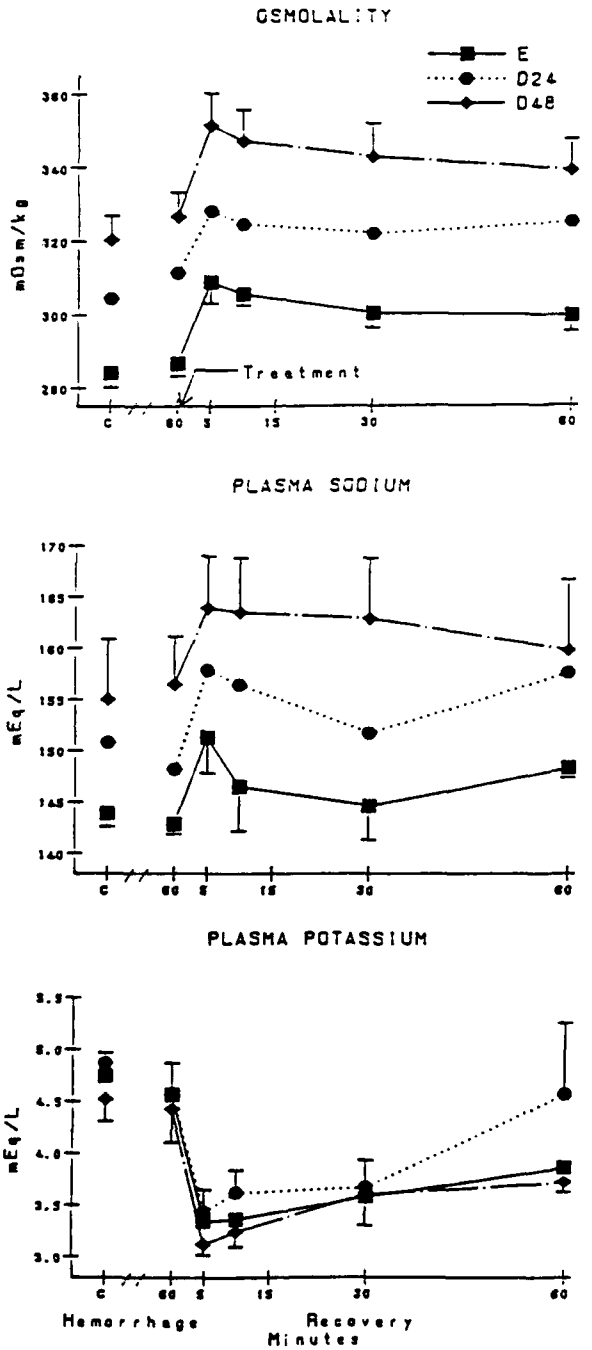

Figure 3: Plasma osmolality and electrolyte concentrations in response to hemorrhage and subsequent resuscitation with HSD in pigs in varying states of hydration. (See Figure 1 legend).

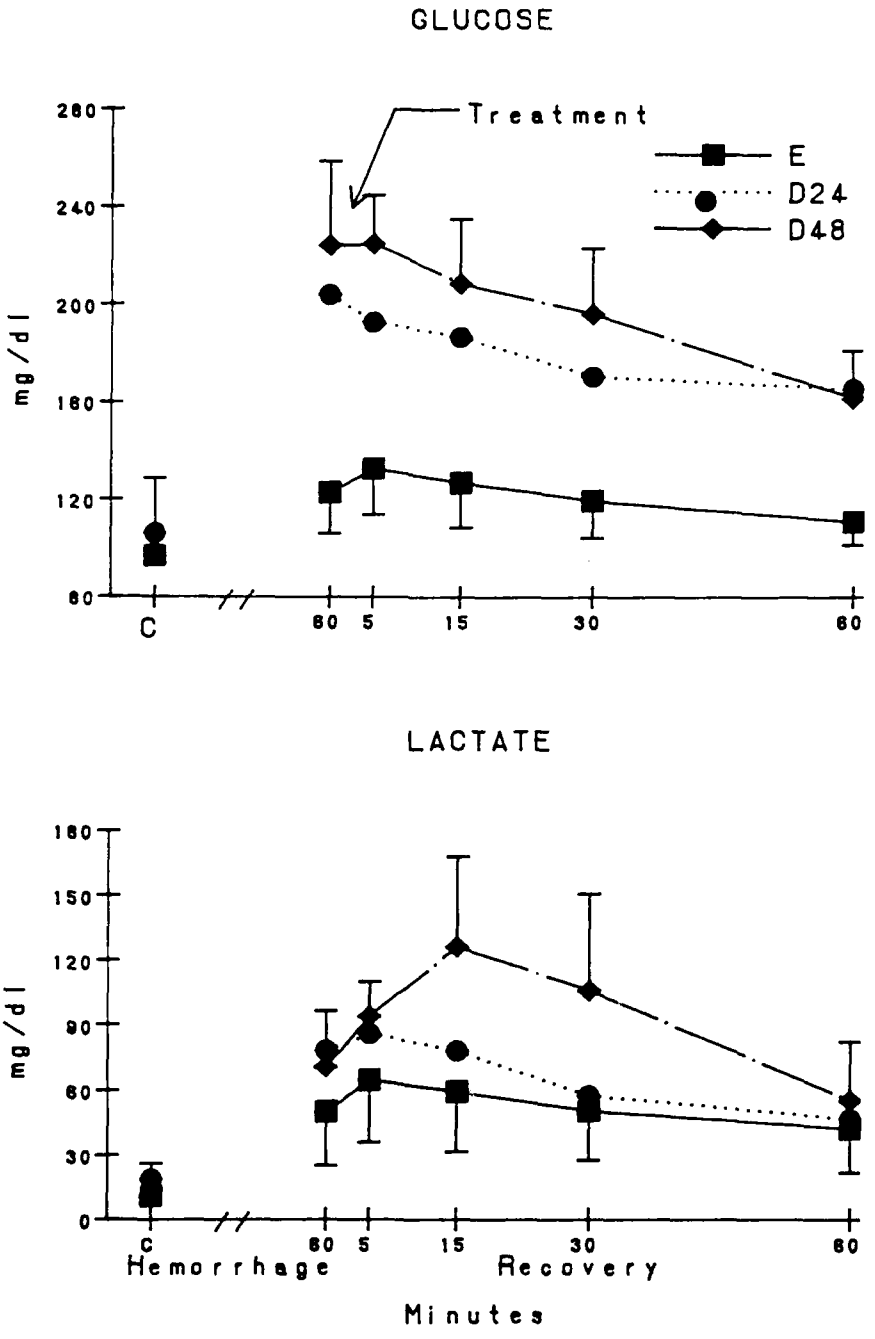

Figure 4: Blood glucose and lactate levels following hemorrhage and resuscitation with HSD in pigs in varying states of hydration. (See Figure 1 legend)

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